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Editorial

Treating the Inflammatory Core of Metabolic Syndromes

Diabetes UK announced on August 17th, 2015 that the number of people living with diabetes in the UK has increased by nearly 60% in the past ten years. Diabetes is also on the rise in the US, with the number of confirmed cases more than tripling between 1980 and 2011 according to the US Centers for Disease control and Prevention (CDC). Worldwide, about 347 million people suffer from this disease, with the vast majority of these cases being attributed to type 2 diabetes (T2D). And in 2012, approximately 1.5 million deaths were directly caused by diabetes according to the World Health Organization (WHO).

Along with the ever-increasing prevalence of diabetes, cardiovascular disease (CVD) remains the number one cause of mortality worldwide, accounting for more than 31% of all global deaths in 2012 (WHO). According to most recent data from the CDC, about 1 in every 4 deaths in the US is currently related to heart disease. Diabetes and CVD are also connected: adults with diabetes are twice to four times as likely to develop CVD than those without diabetes, according to the American Heart Association.

Intertwined with both of these human health catastrophes is the obesity epidemic. Obesity is known to have direct connections to both diabetes and CVD, and it is becoming a global crisis—with more than 600 million people affected around the world, according to 2014 WHO data. Obesity is clearly no longer simply a "first-world" problem.

Metabolic syndrome broadly refers to a set of obesity-related conditions, such as insulin resistance and high-blood pressure, which predispose the patient to increased risk of developing T2D and CVD. What do we know about the mechanistic connections between obesity, diabetes, and CVD, and how can we intervene therapeutically? Several candidate pathways including oxidative stress have emerged as potential targets—with dysregulated reactive oxygen species linked to both insulin-producing pancreatic β-cell failure and cardiovascular disorders. Alterations in the microbiome are also thought to play a role in the metabolic dysregulations associated with obesity. Central to many candidate pathways, however, is a generalized predisposition in the obese patient toward a pro-inflammatory state—including a shift from anti-inflammatory (M2) macrophages to a pro-inflammatory (M1) profile, a decrease in anti-inflammatory regulatory T (Treg) cells in the adipose tissue, and release of pro-inflammatory cytokines directly from the adipocytes.

Pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6 and TNFα are all elevated in obese and T2D patients, and some studies indicate a direct pathogenic role for such molecules in β-cell destruction. In addition to hypertension and dyslipidemia, emerging evidence suggests that the increased inflammation associated with T2D may also directly contribute to the well-documented link between diabetes and CVD.

Managing blood sugar, cholesterol and lipid levels remains the first line of management against these metabolic disorders. However, if T2D and CVD are essentially inflammatory conditions, would addressing this inflammatory core ameliorate symptoms and result in better outcome for patients?

Multiple recent clinical trials have shown that inhibiting IL-1β signaling with anakinra or humanized blocking antibodies (such as gevokizumab or canakinumab) results in a long-term improvement in insulin sensitivity and secretion, and an overall reduction in inflammation. Research is currently underway to determine whether the Nlrp3 inflammasome, which is upstream of IL-1 production and controls its processing and release, may also be a worthwhile target for the treatment of diabetes. Several short-duration clinical studies using TNFα antagonists have not yet found a clear association between blocking TNFα signaling and increased insulin-sensitivity. However, clues from other large-scale clinical trials using TNFα to treat, for example, rheumatoid arthritis show a significant decrease in the development of T2D with treatment. Targeting TNFα may therefore also be worth investigating further as a treatment option for diabetic patients. Recent preclinical studies using a mouse model of T2D have revealed that administration of the anti-inflammatory cytokine IL-33 resulted in a boost in Treg cell populations specifically in the adipose tissue. Inflammation was reduced, and glucose tolerance was restored in the IL-33-treated animals, providing further evidence that targeting inflammatory pathways may have a beneficial effect for diabetic patients.

Heart disease and atherosclerosis, long thought to depend in part on lipid imbalance, are also likely to depend heavily on the inflammatory state of the individual. The inflammation theory of CVD is now rapidly gaining traction, and studies are well underway to determine if modulating the inflammatory pathways dysregulated by metabolic imbalance may improve cardiovascular health. For example, phase III of the large-scale international Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) aims to determine whether blockade of IL-1β can reduce the rates of adverse cardiac events in patients with coronary artery disease and high levels of C-reactive protein (CRP), an inflammatory marker. A second study, the Cardiovascular Inflammation Reduction Trial (CIRT) also aims to test the premise of inflammation theory by treating post-myocardial infarction patients who have either diabetes or metabolic syndrome with methotrexate—a drug which has been shown to reduce IL-6, TNF and CRP. Both of these long-term, large-scale studies are still ongoing, and will soon provide much-anticipated data on whether blocking inflammation can help prevent atherothrombotic events.

Although genetic and large-scale observational studies have demonstrated a definitive association between increased IL-6 expression levels and risk for CVD, targeting IL-6 signaling—for example by using the humanized anti-IL-6R antibody tocilizumab—is likely to be complicated by the fact that IL-6 may have both pro- and anti-inflammatory roles in

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human health. Further studies are needed to determine the degree to which it will be possible to uncouple these IL-6 functions to confer therapeutic benefits.

Obesity and its associated consequences of metabolic dysregulation continue to grow as a world-wide health crisis. Lifestyle changes, including adopting a healthy diet and regular exercise, naturally remain the simplest approach to combating this epidemic. However, better clinical interventions for T2D and CVD patients are still needed, and while they are clearly multifactorial in their etiology, targeting metabolic syndromes at their inflammatory core seems a promising idea well worth pursuing.

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